

784 The Coronary Vasculature and Cardiac Transplantation

Wednesday, March 22, 1995, 10:30 a.m.–Noon
Ernest N. Morial Convention Center, Room 14

10:30

784-1 The Effect of Prenatal Cyclosporine on Fetal Rabbit Growth and the Myocardial Beta Adrenergic Receptor-Cyclic AMP Pathway

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As the pediatric and adolescent survivors of organ transplantation reach reproductive age, there will be an increasing number of fetuses exposed to cyclosporine (CSA) throughout gestation. The effect of CSA on the developing fetus has received little attention. We studied the effect of prenatal CSA administration on fetal rabbits' growth and the myocardial beta adrenergic receptor-cyclic AMP pathway. **Methods:** Pregnant New Zealand white rabbits were treated either with subcutaneous CSA, 20/mg/kg twice weekly, or placebo, starting at 14 days gestation. At 29 days gestation (term 30 days), the fetuses were delivered by cesarian section. Maternal and fetal organs were weighed and fetal myocardium processed and stored. Beta adrenergic receptor numbers were determined by competitive binding assay using radiolabelled Dihydro-alpranolol. Cyclic AMP production was measured using radioenzymatic assay. Statistical comparisons utilized unpaired Student's t-test. **Results:** CSA administration did not alter maternal body or organ growth. In the rabbit pups, body, heart, lung and kidney weights were decreased to 75% of control ($p < 0.0001$). Liver weight was decreased further to 68% of control ($p < 0.0001$ compared to controls, $p < 0.03$ compared to body and other organ weight reductions). Despite the reduction in myocardial growth, beta adrenergic receptor numbers and cyclic AMP production were not different in the CSA treated group. **Conclusions:** Prenatal CSA administration results in asymmetric growth retardation in the rabbit fetus. The beta adrenergic receptor-cyclic AMP pathway does not appear to be altered. **Speculation:** Because CSA is currently not contraindicated during human pregnancy, the effects on the fetus deserve further study.

10:45

784-2 Coronary Vasomotor Responses in Cyclosporine-Treated Piglets

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Chronic treatment with cyclosporine (Cx) seems to produce a decreased ability of the endothelium to secrete nitric oxide. However, its effect on the coronary arterial system remains controversial. Therefore, coronary arteries isolated from piglets treated for 3 weeks with Cx (10 mg/kg/day I.M.; group 1) were studied in organ baths and compared to those isolated from control animals (I.M. injections of the Cx solvent, group 2). On rings contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), the endothelium-dependent relaxations to serotonin (5HT, 1 nM to 0.3 μ M; in the presence of ketanserin 1 μ M), bradykinin (BK, 1 nM to 0.1 μ M), substance P (SP, 0.1 nM to 10 nM) and calcium ionophore (A23187, 1 nM to 1 μ M) were assessed:

Group	Area under curve (AUC)			
	5HT	BK	SP	A23187
1 (n = 12)	479 \pm 24*	158 \pm 18*	198 \pm 8*	217 \pm 10
2 (n = 12)	385 \pm 22	55 \pm 17	145 \pm 12	224 \pm 18

mean \pm SEM; * $P < 0.02$ vs group 2

the maximal relaxation was significantly decreased only for BK (76 \pm 4% vs 92 \pm 4%, % of $PGF_{2\alpha}$ -induced plateau). Depolarization-induced contractions (KCl 90 mM) were similar in both groups whereas the acetylcholine (ACh)-induced contractions (% of KCl 90 mM) were enhanced: the AUC in group 1 was 245 \pm 51 versus 110 \pm 15 in group 2 ($P < 0.01$). After mechanical removal of the endothelium, the increased responsiveness to ACh persisted in group 1. Thus, chronic exposure to Cx impairs receptor-mediated endothelium-dependent relaxations in coronary arteries and also produces functional changes in smooth muscle cells. These alterations may play a role in the occurrence of cardiac graft vasculopathy.

784-3 Prognostic Significance of Intimal Thickening Detected by Intracoronary Ultrasound in Heart Transplant Recipients

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Intracoronary ultrasound (ICUS) is a sensitive tool for the detection of intimal thickening in coronary arteries of heart transplant recipients. However, the prognostic significance of this intimal thickening has not been proven.

During a one year period, 90 transplant recipients had ICUS examination at the time of their annual angiogram. For each ICUS study an intimal index (II), defined as the ratio of the plaque area to the area within the media, was measured for the most diseased segment imaged. The angiogram at the time of ICUS was reviewed for the presence of visually apparent coronary artery disease (V-CAD). Those patients (n = 19) with V-CAD present at the time of ICUS were excluded from the study. The time since transplantation for the 71 pts without V-CAD ranged from 1 to 15 yrs, with a mean of 4.2 yrs and median of 3.9 yrs. The subsequent annual follow-up angiograms of the 71 patients without V-CAD at the time of ICUS were reviewed for the development of V-CAD. Mean duration of angiographic follow-up was 2.0 yrs (range 1–3 yrs).

V-CAD developed on follow-up angiograms in 13 of the 71 pts. Mean time to development of V-CAD was 1.5 yrs. Forty-six patients had II < 0.3 , 4 (9%) of whom subsequently developed V-CAD. Twenty-five patients had II ≥ 0.3 , 9 (36%) of whom developed V-CAD. Odds ratio for future V-CAD between pts with II < 0.3 and II ≥ 0.3 was 5.9 (95% CI 1.8 to 19.0, difference significant at $p < 0.01$ by Fisher's Exact test).

In a subgroup of 22 patients more than 5 years post transplantation at the time of ICUS, 12 had II < 0.3 and 10 had II ≥ 0.3 . In this subgroup none of the 12 pts with II < 0.3 developed V-CAD and only 1 of the 10 with II ≥ 0.3 developed V-CAD (difference not significant).

Conclusion — Among patients more than 1 year and less than 5 years post-transplantation without visually apparent angiographic coronary artery disease, the presence of moderate to severe intimal thickening by ICUS is predictive of the future development of angiographically apparent CAD. Intimal thickening as detected by ICUS is of prognostic significance in patients with angiographically silent transplant coronary artery disease.

11:15

784-4 Older Donor Age Predicts Increased Risk for Coronary Vasculopathy in the Year Following Transplantation: Serial Examination by Intravascular Ultrasound

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Objectives: We have previously shown a high prevalence of transmission of atherosclerosis to recipients examined by intravascular ultrasound within a few weeks of transplantation. However, the effect of donor characteristics on progression of vasculopathy is uncertain.

Methods: We examined 22 patients by intravascular ultrasound within 1.0 \pm 0.2 months after transplantation. Identical sites were imaged again at one year follow-up (12 \pm 0.5 months) to determine donor-related factors associated with the development of intimal thickening during the first year. Intravascular imaging was performed in multiple coronary arteries (2.2 arteries/patient) using a 3.5 Fr, 30 MHz probe. A core laboratory, blinded to patient identity and to time from transplantation, quantified minimum lumen diameter, plaque cross-sectional area, intimal thickness, and percent area reduction.

Results: Donor gender, hypertension and smoking did not predict progression of vasculopathy in the first year. However, older donor age was a strong predictor of measures of disease progression.

Donor Group:	Increase in Intimal Thickness (mm)	Plaque Area (mm ²)	Area Reduction (%)
Age < 35	0.12	0.63	4.7
Age > 35	0.28	2.08	10.3
P value	<0.008	<0.001	<0.024

Conclusions: Recipients of older donor hearts develop more intimal thickening in the first year following transplantation. Longer follow-up will be required to prove that this increase in intimal thickness correlates with the subsequent development of severe vasculopathy. These findings have implications for donor organ acceptance criteria.